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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/816,814	03/23/2001	Jorg J. Goronzy	07039-251001	6147

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EXAMINER
BASI, NIRMAL SINGH

ART UNIT	PAPER NUMBER
1646	14

DATE MAILED: 05/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/816,814	Goronzy et al
Examiner	**Art Unit**
Nirmal S. Basi	1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Dec 23, 2002*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above, claim(s) *34 and 35* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-33* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 7
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Response to Restriction mailed January 14. 2003 (paper number 12) has been entered.

2. ***Election/Restriction***

Applicant's election without traverse of Group I, claims 1-33 in Paper No. 9 (7/22/02) and election of Species I (CD21L polypeptide), without traverse, in paper No. 12 (2/7/03) is acknowledged. Claims 34-35 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected.

3. **Objections**

Applicants are required to use the heading "Brief Description of the Drawings" to describe the drawings. See MPEP 608.01(f). On page 6, Applicant has written "DESCRIPTION OF DRAWINGS"

Appropriate correction is required.

Claim Rejection, 35 U.S.C. 112

4. Claims 1-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 8, 13, 23 are indefinite because it is not clear what is a "chemoattractant polypeptide" so as to allow the metes and bounds of the claims to be determined. The term "chemoattractant polypeptide" is a functional term and provides no information as to the

structure of the polypeptide. It is not clear which polypeptides are classified as chemoattractant polypeptides and what they are attracted to.

Claims 9 and 24 are indefinite because it is not clear what is a "B-chemoattractant polypeptide" so as to allow the metes and bounds of the claims to be determined. The term "B-chemoattractant polypeptide" is a functional term and provides no information as to the structure of the polypeptide. It is not clear which polypeptides are classified as B-chemoattractant polypeptides so as to allow the metes and bounds of the claim to be determined.

Claim 12 recites the limitation "sample contains at least four said markers" in line 2 of the claim. Claim 12 depends on claim 1. There is insufficient antecedent basis for this limitation in the base claim. Base claim 1 only lists 3 markers.

Claim 32 recites the limitation "sample contains at least four said markers" in line 2 of the claim. Claim 32 depends on claim 13. There is insufficient antecedent basis for this limitation in the base claim. Base claim 13 only lists 3 markers. Similarly claim 33 recites the limitation "sample contains at least four said markers". Claim 33 depends on claim 32 which depends on claim 13. There is insufficient antecedent basis for this limitation in the base claim. Base claim 13 only lists 3 markers.

Claims 2-7, 10-11, 14-22 and 25-31 are rejected for depending upon an indefinite base (or intermediate) claim and fail to resolve the issues raised above.

Claim Rejection, 35 U.S.C. 112

5. Claims 1-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for determining the severity of a rheumatoid arthritis (RA) condition in a mammal, said method comprising determining whether or not a sample of synovial tissue from said mammal contains at least one marker, said marker being an elevated level of CD21L polypeptide, lymphotoxin α (LT-α), lymphotoxin β (LT-β), B-lymphocyte chemoattractant (BLC), secondary lymphoid tissue cytokine (SLC), dendritic cell-derived C-C chemokine (DC-CK 1) or macrophage chemoattractant protein-1 (MCP-1) and those markers in the prior art that are elavated in RA, wherein the presence of said at least one marker indicates that said arthritis condition is severe, does not reasonably provide enablement for use of other markers to indicate that said arthritis condition is severe. The, specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification discloses:

A) Synovial tissue samples obtained from 64 patients with active rheumatoid arthritis (RA) were grouped into three categories based on lymphoid organization. The first category (36 samples, 56.3%) contained diffuse infiltration of T cells and B cells (no lymphoid organization). The second category (13 samples, 20.3%) contained samples with B cell-T cell follicles lacking germinal centers (GC^- follicles). The third category (15 samples, 23.4%) contained samples with GC-positive B cell-T cell follicles (GC^+ follicles). RNA was isolated from the 64 samples

listed above and used in RT-PCR with primers designed to amplify CD21L sequences. Amplified products corresponding to CD21L were detected in 15 of the 64 samples, said samples corresponding to cells organized into GC^+ follicles. No CD21L signal was detected in the remaining 49 of 64 samples. Therefore the results demonstrate that the presence of CD21L in a sample can be used to predict the presence of GC^+ follicles and as a marker for RA condition.

B) Total RNA described in A above was amplified by PCR with primers for lymphotoxin α (LT-α), lymphotoxin β (LT-β), B-lymphocyte chemoattractant (BLC), secondary lymphoid tissue cytokine (SLC), dendritic cell-derived C-C chemokine (DC-CK 1) macrophage chemoattractant protein-1 (MCP-1). Samples with GC^+ follicles were found to contain higher levels of LT-α and LT-β transcripts when compared with to the levels measured in either samples with GC^- follicles or samples with no lymphoid organization. In samples with GC^+ follicles the median LT-α and LT-β transcript numbers were 182 and 441, respectively. In samples with GC^- follicles the median LT-α and LT-β transcript numbers were 42 and 35, respectively. In samples with no lymphoid organization the median LT-α and LT-β transcript numbers were 10 and 43, respectively. Samples with GC^+ follicles were also found to contain higher levels of BLC and SLC transcripts when compared with to the levels measured in either samples with GC^- follicles or samples with no lymphoid organization. In samples with GC^+ follicles the median BLC and SLC transcript numbers were 2139 and 212, respectively. In samples with GC^- follicles the median BLC and SLC transcript numbers were 159 and 124, respectively. In samples with no lymphoid organization the median BLC and SLC transcript numbers were 97 and 88,

respectively. Further high levels of DC-CK 1 and MCP-1 were predictive of GC^+ follicles. Therefore the results demonstrate that the presence of LT-α, LT-β, BLC, SLC DC-CK 1 and MCP-1 in a sample can be used to predict the presence of GC^+ follicles and as a marker for RA condition.

While the person of ordinary skill in the art would, in light of the specification be able to use the markers listed above, or known in the prior art, as predictive for the RA condition, the scope of the claims, which encompass other polypeptides in the genus of chemoattractant polypeptides are not enabled by the disclosure. The specification and prior state that the etiopathogenesis of the RA syndrome is not well understood (specification page 1, last paragraph) and results obtained in the art can be sometimes contradictory and confusing in nature (Fox et al. IDS ref AJ, page 599, last two paragraphs). Further Goronzy et al (IDS ref. AK, page 657, last paragraph) show the complex nature of RA and the difficulty in obtaining a working model upon which to base predictions. Goronzy states, "It is possible that the predictions from the animal models of antigen-specific autoimmunity cannot easily be generalized to a heterologous human population and patients with RA therefore may use completely different T-cell receptor structures in response to an autoantogen---". Further Goronzy states that the role of T lymphocytes in the pathogenesis of RA remains elusive (page 669, second paragraph). Therefore due the complex nature of RA it would require trial and error experimentation, ie undue experimentation, to determine other chemoattractant polypeptides encompassed by the claim. Therefore, since the presence of elevated levels of all chemoattractant polypeptides is not

predicative of a RA condition it would require extensive, undue experimentation to determine which polypeptides would serve as positive markers in the claimed method. The specification provides no structural information upon which to search for additional chemoattractant polypeptides that could be used in claimed method, only functional guidance is provided. Further the scope of the claims is not limited to measuring levels of markers in the synovial tissue sample for use in claimed method. The specification discloses markers were measured in the synovial fluid and there is no indication that other tissues would show the same pattern of expression of said markers so as to indicate a RA condition. RA is a chronic destructive disease characterized by inflammatory response in the synovium. For example brain tissue and blood sample, when compared to synovial fluid, would not be expected to have the same pattern of expression of markers indicative of a RA condition

Further, the disclosure does not teach how to isolate other markers that would be predictive of the RA condition, or any naturally occurring mutants of CD211, LT-α, LT-β, BLC, SLC DC-CK 1 and MCP-1 which could be used as markers to predict the RA condition. Further the markers measured in claimed method are only useful in determining rheumatoid arthritis and not other forms of arthritis as encompassed by the claims. The factors associated with all forms of arthritis are not the same and there is no disclosure that the markers for RA would also be predictive of other forms of arthritis.

Therefore due to the large quantity of experimentation necessary to identify chemoattractants polypeptides encompassed by the claims, the lack of direction/guidance

presented in the specification regarding the identification, purification, isolation and characterization of said polypeptides, and the breadth of the claim which fail to limit tissue sample to synovial tissue, undue experimentation would be required of the skilled artisan to make or use the claimed invention in its full scope. Therefore the scope of the claims is enabled for those markers which are indicative of the rheumatoid arthritis (RA) condition, ie. disclosed in Examples 1-4, present in the prior art and which are indicative of the rheumatoid arthritis (RA) condition, and also when the tissue sample is limited to synovial tissue.

6. **Claim Rejections, 35 U.S.C. 103**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 7-20, 22-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goronzy et al (US Patent No. 6555,320 B1) in view of Li et al (US Patent No. 6,075,124) and further in view of Karin et al (US Patent 6,075,124), Kara et al (US Patent 6,088,695) and Coli et al (US Patent 6,018,713) . Goronzy teaches an invention involving methods and materials for evaluating rheumatoid arthritis (RA)in a patient and specifically classifying a RA condition as diffuse, follicular, or granulomatous. In addition, the invention provides methods and materials for determining if an individual suffering from a rheumatoid arthritis condition will develop severe disease (see abstract). Goronzy discloses RA is systemic inflammatory disease that primarily manifests as synovial inflammation of diarthrodial joints and the level of particular cytokines within tissue can be used to classify a RA condition, the granulomatous patients being more susceptible to severe RA disease. The cytokines, Il-4, Il-10 and IFN-γ, Il-1β, TNF-α and TBF-1 were used to determine the severity of RA in a patient by comparing to a reference level (column 3, Table 7 and claims). Goronzy does not disclose a method of assisting a person in determining the severity of an arthritis condition in a mammal or communicating information about the presence or absence of said at least one marker in said sample to said person, wherein the presence of said at least one marker indicates that said arthritis condition is severe. Further Goronzy does not specifically disclose that the presence of at least on marker indicates that the RA condition is severe.

Li teaches MCP-1(monocyte chemotactic protein) levels were found to be significantly higher in synovial fluid from RA patients compared to synovial fluid form osteoarthritis patients or from patents with other arthritides (column 2).

Karin discloses the use of cytokines, MIP-1α, MCO-1, MIP-1β, RANTES and TNF-α, to treat RA by inducing formation of antibodies to said cytokines, wherein said antibodies reduce an vivo activity of an endogenous cytokine of said cytokines, to thereby treating RA (see claims and Examples). Karin also discloses the use of rats in evaluating the effects of cytokines in RA treatment.

Kara teaches a system and method for communicating medical records. It is also disclosed patients undergo tests, the results of which are gathered by the diagnosing physician and then evaluated.

Coli et al discloses an integrated system and method for ordering and cumulative results reporting of medical tests. , above.

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to use the chemoattractant polypeptides (cytokines) disclosed above by Goronzy, Li and Karin to determine the severity of RA in a mammal said method comprising determining whether or not a sample from said mammal contains at least one marker, Il-4, Il-10 and IFN-γ, Il-1β, TNF-α and TBF-1 (Goronzy), MCP-1 (Li) or MIP-1α, MCO-1, MIP-1β, RANTES and TNF-α (Karin) wherein the presence of at least one marker indicates that said arthritis condition is severe and further communicating information about the presence or

absence of said at least one marker in said sample to a person (doctor scientist etc) as disclosed by Kara et al and Coli et al. The ordinary artisan would have been motivated to measure the levels of the markers Il-4, Il-10 and IFN-γ, Il-1β, TNF-α, TBF-1, MCP-1, MIP-1α, MCO-1, MIP-1β, RANTES in a mammal synovial tissue sample because prior art teaches that elevation of said markers, either alone or in combination is an indicator of the severity of the RA condition. Further measurement of the markers Il-4, Il-10 and IFN-γ, Il-1β, TNF-α, TBF-1, MCP-1, MIP-1α, MCO-1, MIP-1β, RANTES is well known in the art and is routinely carried out by laboratory technicians. Laboratory technicians routinely report their results to the medical doctor who in turn evaluates the results and informs the patient of the test results. The protocol of testing samples for chemokines, reporting the results to a physician (directly or indirectly), evaluating the results and then communicating the results to other parties (directly or indirectly is well known in the art) and is exemplified by Kara et al and Coli et al.

The ordinary artisan would have expected success for determining the severity of RA by measuring the markers Il-4, Il-10 and IFN-γ, Il-1β, TNF-α, TBF-1, MCP-1, MIP-1α, MCO-1, MIP-1β, RANTES because said markers have been associated with RA and antibodies to some of said markers have been used to treat RA. Further the method of Kara and Coli could be used to communicate the results of the severity of RA analysis because they relate to an improved system and method for on-line ordering of medical tests in a health care network and method for uniformly recording and reporting test results.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nirmal Basi whose telephone number is (703) 308-9435. The examiner can normally be reached on Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for this Group is (703) 308-0294.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Nirmal S. Basi
Art Unit 1646
May 19, 2003

YVONNE EYLER, PH.D
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